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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,138	08/28/2001	Mark Kunkel	13162	5900

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,138	KUNKEL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 28, 2001 and January 29, 2002. Currently, claims 1-47 are pending.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3, 18, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 3, 18 are indefinite because it is unclear how one chain terminating nucleotide can have the same detectable characteristic. It is unclear what the single chain terminator must have the same characteristic with. In the event that the claim is directed to when there are more than one chain terminating, the claim could be amended to recite, more than one chain terminating nucleotide.

B) Claim 46 is indefinite because Claim 1 does not contain a step (e). It is unclear whether the claim is directed to a further comprising step or whether the claim has misidentified a step.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 13-14, 39, 43-45, 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Damiani et al. (Animal Genetics, Vol. 23, No. 6, pages 561-566, 1992).

Damiani et al. (herein referred to as Damiani) teaches a method of identifying one or more nucleotides present at a polymorphic site using bi-directional allele specific polymerase chain reaction, namely identifying a variant of the bovine B-casein gene in exon VII (abstract). Damiani teaches using a fast and reliable procedure for genotyping the B and non-B alleles of the B-casein gene. Damiani teaches using both allele specific primer and non-specific primers in a single reaction (see Figure 1). Damiani obtains an upper strand and a lower strand of the B-casein B-variant using outer primers, namely PB1 and PB2 (limitations of Claim 1a, 39a, 47a)(limitations of Claims 43-45). Damiani teaches hybridizing allele specific primers, namely PB4 and PB3, to the upper strand and the lower strand in a single reaction with PB1 and PB2 (limitations of Claim 1b, 14, 39b, 47b). The bi-directional allele specific PCR reaction employed dNTPs and the four primers (limitations of Claim 1c, 39c, 47c). The amplification products were distinguished by gel electrophoresis in agarose gel with ethidium bromide

(limitations of Claim 1d, 39d, 47d). Damiani teaches that in BAS-PCR amplification of at least one diagnostic fragment occurs regardless of the genotype, thus providing a positive control for the reaction (page 564). Damiani teaches that the technique works with whole blood, or washed blood cells (limitations of Claim 13)(page 564). Therefore, since Damiani teaches every limitation of the claims, Daiani anticipates the claimed invention.

4. Claims 1, 13-15, 39, 43-45, 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu et al. (US Pat. 6,207,425, filed September 10, 1998).

Liu et al. (herein referred to as Liu) teaches bi-directional polymerase chain reaction (PCR) amplification of specific alleles (Bi-PASA). Liu teaches using two outer primers (P and Q) and two inner primers (A and B). As seen in Figure 1, three possible fragments may be amplified using the P, Q, A and B primers. Liu obtains an upper strand and a lower strand of nucleic acid using outer primers, namely P and Q (limitations of Claim 1a)(limitations of Claims 43-45). Liu teaches hybridizing allele specific primers, namely A and B, in a single reaction with P and Q (limitations of Claim 1b, 14). The bi-directional allele specific PCR reaction employed dNTPs and the four primers (limitations of Claim 1c). The amplification products were distinguished by gel electrophoresis in agarose gel with ethidium bromide (limitations of Claim 1d). Liu teaches that the Bi-PASA method is rapid, reproducible, inexpensive, non-isotopic and amenable to automation (col. 2, lines 60-64). Liu teaches amplifying genomic DNA (col.

5, lines 46-48). Therefore, since Liu teaches every limitation of the claims, Liu anticipates the claimed invention.

5. Claims 1-4, 8-19, 23-29, 39, 42-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Huang et al (US Pat. 6,287,778, September 11, 2001).

Huang et al. (herein referred to as Huang) teaches a method of allele detection using primer extension with sequence-coded identity tags. As seen in Figure 2, a nucleic acid may be amplified by PCR, followed by a primer extension reaction and subsequent capture on a solid support. The primer containing a tag at its 5' end, terminates in a 3' nucleotide at the polymorphic locus (col. 3, lines 10-15). The final step is a hybridization of the labeled extension product to a solid support to which a probe is attached that is complementary to the tag at the 5' end of the extension primer. Huang teaches that the primer extension step utilizes two different primers which each hybridize to opposite strand of an amplified double stranded DNA. Each primer terminates at the polymorphic locus. The primer extension reaction may be more robust with one strand as a template than the other. In addition, the information obtained from the second strand should confirm the information obtained from the first strand (limitations of Claim 1a, b, c). The primers can be the same or different 5' tags (col. 9, lines 1-10)(limitations of Claim 1d, 8-9). Huang teaches the length of the tag probe is at least 12-40 nucleotides in length (col. 4, lines 43-46)(limitations of Claim 10). Huang teaches that the primer extension step may use dideoxynucleotides to permit only the addition of a single nucleotide to the prier in a single-base extension reaction (col. 8,

lines 58-60)(limitations of Claim 2, 4). Huang teaches that the nucleotides added by the primer extension reaction are labeled (col. 9, lines 15-20)(limitations 3). Huang teaches that two different fluorescent labels can be used to distinguish two alleles at each polymorphic locus examined (col. 17, lines 55-58). Huang teaches one specific example of a solid support is a glass surface, an array, microarray, high density array, bead, or microtiter dish (col. 12, lines 65-67; col. 5, lines 45-48)(limitations of Claim 11, 15). Huang teaches that the DNA in the sample may be of any source including genomic, nuclear, cDNA, mitochondrial (col. 4, lines 63-68)(limitations of claim 13). Therefore, since Huang teaches every limitation of the claims, Huang anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 5-7, 20-22, 30-38, 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (US Pat. 6,287,778, September 11, 2001) in view of Goelet et al. (US Pat. 5,888,819, March 30, 1999).

Huang et al. (herein referred to as Huang) teaches a method of allele detection using primer extension with sequence-coded identity tags. As seen in Figure 2, a nucleic acid may be amplified by PCR, followed by a primer extension reaction and subsequent capture on a solid support. The primer containing a tag at its 5' end, terminates in a 3' nucleotide at the polymorphic locus (col. 3, lines 10-15). The final step is a hybridization of the labeled extension product to a solid support to which a probe is attached that is complementary to the tag at the 5' end of the extension primer. Huang teaches that the primer extension step utilizes two different primers which each hybridize to opposite strand of an amplified double stranded DNA. Each primer terminates at the polymorphic locus. The primer extension reaction may be more robust with one strand as a template than the other. In addition, the information obtained from the second strand should confirm the information obtained from the first strand (limitations of Claim 1a, b, c; 39a, b, c; 47a, b, c). The primers can be the same or different 5' tags (col. 9, lines 1-10)(limitations of Claim 1d, 8-9, 39d, 47d). Huang teaches the length of the tag probe is at least 12-40 nucleotides in length (col. 4, lines 43-46)(limitations of Claim 10). Huang teaches that the primer extension step may use dideoxynucleotides to permit only the addition of a single nucleotide to the prier in a

single-base extension reaction (col. 8, lines 58-60)(limitations of Claim 2, 4). Huang teaches that the nucleotides added by the primer extension reaction are labeled (col. 9, lines 15-20)(limitations 3). Huang teaches that two different fluorescent labels can be used to distinguish two alleles at each polymorphic locus examined (col. 17, lines 55-58). Huang teaches one specific example of a solid support is a glass surface, an array, microarray, high density array, bead, or microtiter dish (col. 12, lines 65-67; col. 5, lines 45-48)(limitations of Claim 11, 15). Huang teaches that the DNA in the sample may be of any source including genomic, nuclear, cDNA, mitochondrial (col. 4, lines 63-68)(limitations of claim 13).

Huang does not specifically teach using all four labeled terminator nucleotides.

However, Goelet et al. (herein referred to as Goelet) teaches contacting a primer with a nucleic acid of interest with a reagent containing four labeled terminators, each terminator being labeled with a different detectable marker (limitations of Claim 5, 20). Goelet teaches that the duplex of primer and nucleic acid is contacted under conditions permitting base pairing of a complementary terminator present in the reagent with the nucleotide base to be identified. Goelet teaches that the identity of the detectable marker preset at the 3' end of the extended primer is determined to identify the terminator and in turn the allele present in the target (col. 9, lines 35-50). Goelet teaches that the detectable markers attached to the terminators is an isotopically labeled moiety, a chromophore, a fluorophore, a protein moiety, or a moiety to which an isotopically labeled moiety, chromophore, fluorophore or a protein moiety can be

attached. The reagent may also be different detectable fluorophores (col. 8, lines 50-60)(limitations of Claim 6-7, 21-22).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the primer extension method of Huang with the teachings of Goelet. Huang teaches adding two different nucleotides differentially labeled to determine the allele present. Goelet further teaches that all four labeled terminators may be added to a primer extension method. The ordinary artisan would have recognized that the addition of all four labeled terminators, as taught by Goelet, would have the expected advantage, over the method of Huang, of facilitating a single reaction for the detection of all possible alleles. The ordinary artisan would have been motivated to have added all possible labeled terminators to the method of Huang to allow the simultaneous detection of each of the possible nucleotides. Since Huang only teaches using two labeled terminators in the same reaction, in order to determine the presence of all of the various nucleotides, Huang would be required to perform his method twice to perform a complete evaluation of all four nucleotides possible at a particular position. However, the method of Goelet allows the ordinary artisan to perform a single reaction to determine the frequency of all possible nucleotides at a particular position. This ability to detect all possible nucleotides in a single reaction saves not only time, but also reagents. Therefore, it would have been prima facie obvious for the ordinary artisan to have added all possible terminator nucleotides, labeled to the method of Huang for the expected benefits of saving time and reagents.

Conclusion

8. No claims allowable over the art.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Ye et al. (Nucleic Acids Research, Vol. 20, No. 5, pages 1152, 1992). Ye teaches allele specific amplification by tetra-primer PCR. Ye does not teach primers which hybridize immediately adjacent to the polymorphic site, but rather teaches a set of primers where the mismatched residue is in the middle of the internal primers (Figure 1).

B) Ffrench-Constant et al (US Pat. 6,008,046, December 28, 1999) teaches that either the forward or the reverse primer gave stronger discrimination in allele specific PCR primers (col. 30-31).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
February 5, 2003

Jehanne Souaya

JEHANNE SOUAYA
PATENT EXAMINER

2/5/03